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**Title: Statistical power of clinical trials has increased while effect size remained stable: an
empirical analysis of 136,212 clinical trials between 1975-2014**

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29 **Abstract**

30 **Objective.** To study the statistical power of randomized clinical trials and examine
31 developments over time.

32 **Study Design and Setting.** We analysed the statistical power in 136,212 clinical trials between
33 1975 and 2014 extracted from meta-analyses from the Cochrane database of systematic reviews.
34 We determined study power to detect standardized effect sizes, where power was based on the
35 meta-analysed effect size. Average power, effect size and temporal patterns were examined for
36 all meta-analyses and a subset of significant meta-analyses.

37 **Results.** The number of trials with power $\geq 80\%$ was low (7%) but increased over time: from 5%
38 in 1975–1979 to 9% in 2010–2014. In significant meta-analyses, the proportion of trials with
39 sufficient power increased from 9% to 15% in these years (median power increased from 16% to
40 23%). This increase was mainly due to increasing sample sizes, whilst effect sizes remained
41 stable with a median Cohen's h of 0.09 (IQR 0.04-0.22) and a median Cohen's d of 0.20 (0.11-
42 0.40).

43 **Conclusion.** This study demonstrates that sufficient power in clinical trials is still problematic,
44 although the situation is slowly improving. Our data encourage further efforts to increase
45 statistical power in clinical trials to guarantee rigorous and reproducible evidence-based
46 medicine.

47 **Key words:** statistical power; clinical trial; randomized

48 **Running title:** Statistical power in clinical trials over time

49 **Word count:** 198 (abstract), 2125 (body)

50 **What is new?**

- 51 • Study power in clinical trials is low: 7% of trials were sufficiently powered (≥ 0.8) and
52 14% had a power above 0.5; within significant meta-analyses 12% was sufficiently
53 powered and 24% had a power above 0.5.
- 54 • Study power has increased from 5% in 1975–1979 to 9% in 2010–2014.
- 55 • Average effect sizes are small and did not increase over time.
- 56 • When determining the required sample size of a clinical trial, small effects should be
57 assumed to ensure an adequate sample size.

1. Introduction

The practice of conducting scientific studies with low statistical power has been consistently criticized across academic disciplines¹⁻⁵. Statistical power is the probability that a study will detect an effect when there is a true effect to be detected. Underpowered studies have a low chance of detecting true effects and have been related to systematic biases including inflated effect sizes and low reproducibility^{6,7}. Low statistical power has been demonstrated, amongst others, in the fields of neuroscience, economics and psychology^{4,8-10}. For clinical trials in the field of medicine, the issue of sample size evaluation and statistical power is essential since clinical decision making and future research are based on these clinical trials^{11,12}. Moreover, low power in clinical trials may be unethical in light of the low informational value from the outset while exposing participants to interventions with possible negative (side) effects¹. Also in medical research statistical power is low^{3,8}, but a systematic overview of temporal patterns of power, sample sizes, and effect sizes across medical fields does not exist. In the current study, we provide a comprehensive overview of study power, sample size, and effect size estimates of clinical trials published since 1975 which are included in the Cochrane database of systematic reviews, and analyse emerging trends over time.

2. Materials and Methods

Data were extracted and calculated from trials included in published reviews from the second Issue of the 2017 Cochrane database of systematic reviews. Cochrane reviews only include meta-analyses if the methodology and outcomes of the included trials are comparable across study populations. Meta-analysis data is available for download in standardized XML-format for those with an institutional Cochrane Library license. We provide open-source software to convert these data and reproduce our entire processing pipeline ¹³.

Trials were selected if they were published after 1974 and if they were included in a meta-analysis based on at least five trials. Since relatively few studies from 2015-2017 were included in our meta-analyses, these years were excluded. For each individual clinical trial, publication year, outcome estimates (odds or risk ratio, risk difference or standardized mean difference) and group sizes were extracted. For the main analyses all meta-analyses were used; sub-analyses were performed on only the meta-analyses with a reported p-value below 0.05, irrespective of the p-value of the individual trial. For meta-analyses reporting standardized mean differences (Cohen's d), the reported meta-analytic effect size was used to compute individual study power. For meta-analyses reporting dichotomous outcomes, meta-analytic effect size (Cohen's h) was computed using arcsine transformation of proportions ¹². The main analysis used the effect size extracted from the meta-analysis, which was performed as either fixed-, or random-effects as judged by the authors of that specific Cochrane review. As a sensitivity analysis we recomputed the meta-analytic effect size using fixed effects, random effects, and unrestricted weighted least squares/ weighed average of the adequately powered (WLS-WAAP) ¹⁴. This latter method was developed to optimize results from meta-analysis in the context of selective reporting bias: WLS-WAAP performs better than both fixed and random effects analyses in the context of publication

97 bias, allows to correct for heterogeneity, and gives similar results to fixed effects when both are
98 not present ^{14,15}. Study power was computed in R using the ‘pwr’ package ¹⁶. Following
99 minimum recommendations for the statistical power of studies ¹², comparisons with a power
100 above or equal to 80% were considered to be sufficiently powered. Study power, group sizes and
101 effect sizes over time were summarised and visualized for all clinical trials.

3. Results

Data from 136,212 clinical trials were available, from 11,852 meta-analyses in 1,918 Cochrane reviews. Of these, 77,947 trials (57.2%) were from a meta-analysis with an overall p-value below 0.05, from 5,903 meta-analyses (49.8%) in 1,411 Cochrane reviews (73.6%). In the original systematic reviews fixed effects were used in 55% of meta-analyses whereas 45% used random effects. Of all trials 7.3% had a statistical power of at least 80% (the recommended minimum¹², which we shall denote as ‘sufficient power’) to detect an effect size as large as the meta-analysed effect size; for the subset of significant meta-analyses this was 12.4%. The median power (interquartile range, IQR) was 9% (95% confidence interval (CI) 6-26%), which was 20% (10-48%) for significant meta-analysis (Table 1).

Table 1 | Proportion studies with sufficient power and median power.

| Selected meta-analyses | N meta-analyses (N studies) | Sufficient (≥ 0.8) power (95% CI) | Median power (IQR) |
|------------------------|--------------------------------|---|-----------------------|
| All | 11,852 (136,212) | 7.3 (7.2-7.5) | 0.09 (0.06-0.26) |
| Significant | 5,903 (77,947) | 12.4 (12.2-12.7) | 0.20 (0.10-0.48) |

CI: confidence interval. FE: fixed effects. IQR: interquartile range.

Between 1975–1979 and 2010–2014 the proportion of sufficiently powered studies rose from 5.1% (4.3-6.1) to 8.5% (8.0-8.9) (Figure 1, top right) while the median power changed from 0.09 (IQR 0.06-0.26) to 0.10 (IQR 0.06-0.30) (Figure 1, left). Within significant meta-analyses the rise was more clear: study power increased with the median rising from 16% (IQR 10-39) to 23% (IQR 12-55) (Supplementary Figure 1, left), and the proportion of sufficiently powered studies from 9.0% (7.6-10.6) to 14.7% (13.9 - 15.5) (Supplementary Figure 1, top right). This trend is seen across medical disciplines (Supplementary Figure 2). When the threshold for sufficient power is set at a minimum of 50% power, the proportion of trials with sufficient power

is still low but also rising (Supplementary Figure 3). The distribution of power showed a bimodal pattern, with many low-powered studies and a small peak of studies with power approaching 100% (Figure 1 and Supplementary Figure 1, bottom right).

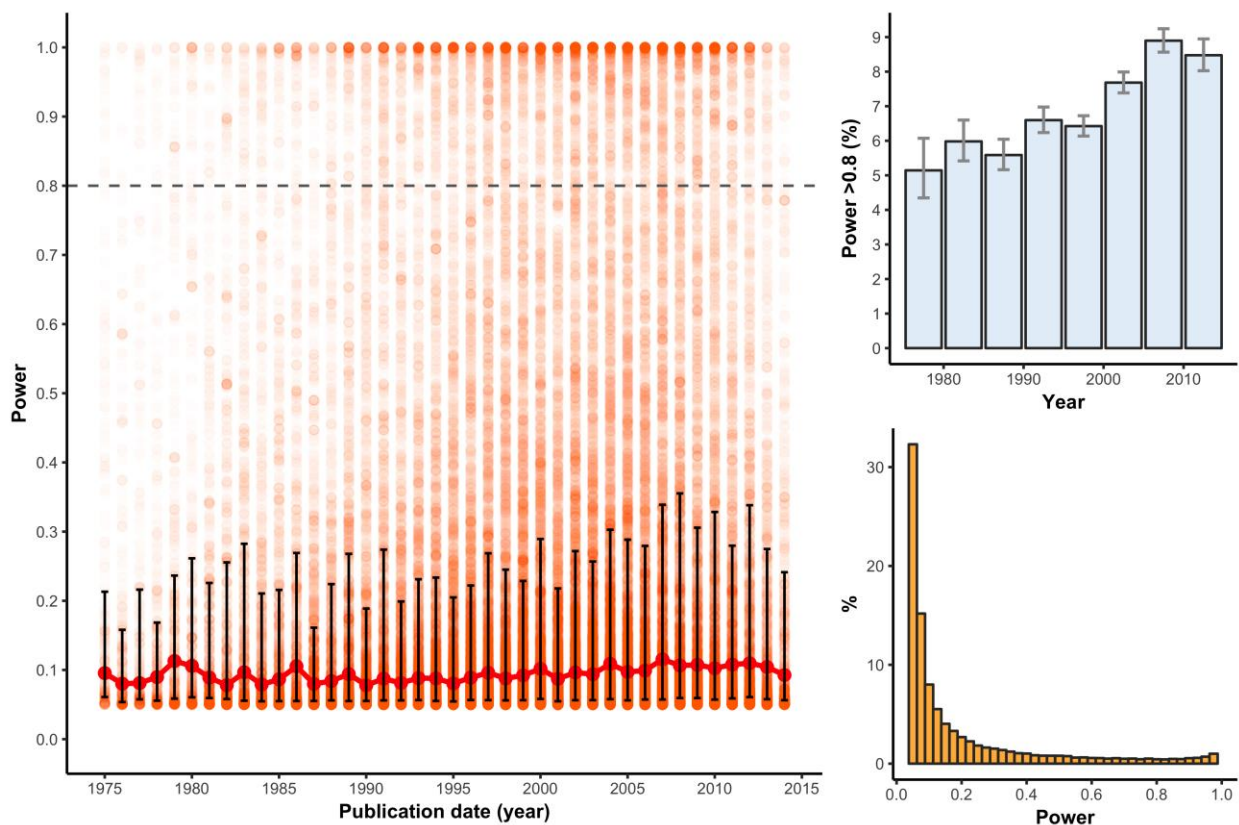


Figure 1 | Statistical power of clinical trials between 1975 and 2014 (left). Individual comparisons are shown as semi-transparent dots. Median power is shown in red with interquartile range as error bars. The percentage of adequately powered trial comparisons (i.e. $\geq 80\%$ power) is increasing over time (top right). The biphasic power distribution of the trials in general is apparent (bottom right).

The average number of participants enrolled in a trial arm increased over time (Figure 2, top left). The median group size in 1975–1979 ranged between 30 and 45; for the years 2010–2014 the median group size was between 74 and 92. The median effect sizes are summarized in Table 2; these remained stable over time (Figure 2). The standardized effect sizes were small, with a median Cohen’s h of 0.09 (0.04-0.22) and a median Cohen’s d of 0.20 (0.11-0.40) (Table 2); Figure 3 shows the distribution plots for these two measures; for the significant meta-analyses the median effect sizes were higher (Supplementary Table 1 and Supplementary Figure 4). Sensitivity analyses showed robust results regardless of the method for performing meta-analysis. The proportion of studies with sufficient power was between 7.2% and 7.5% depending on the method; the median power remained 9% across methods (Supplementary Table 2).

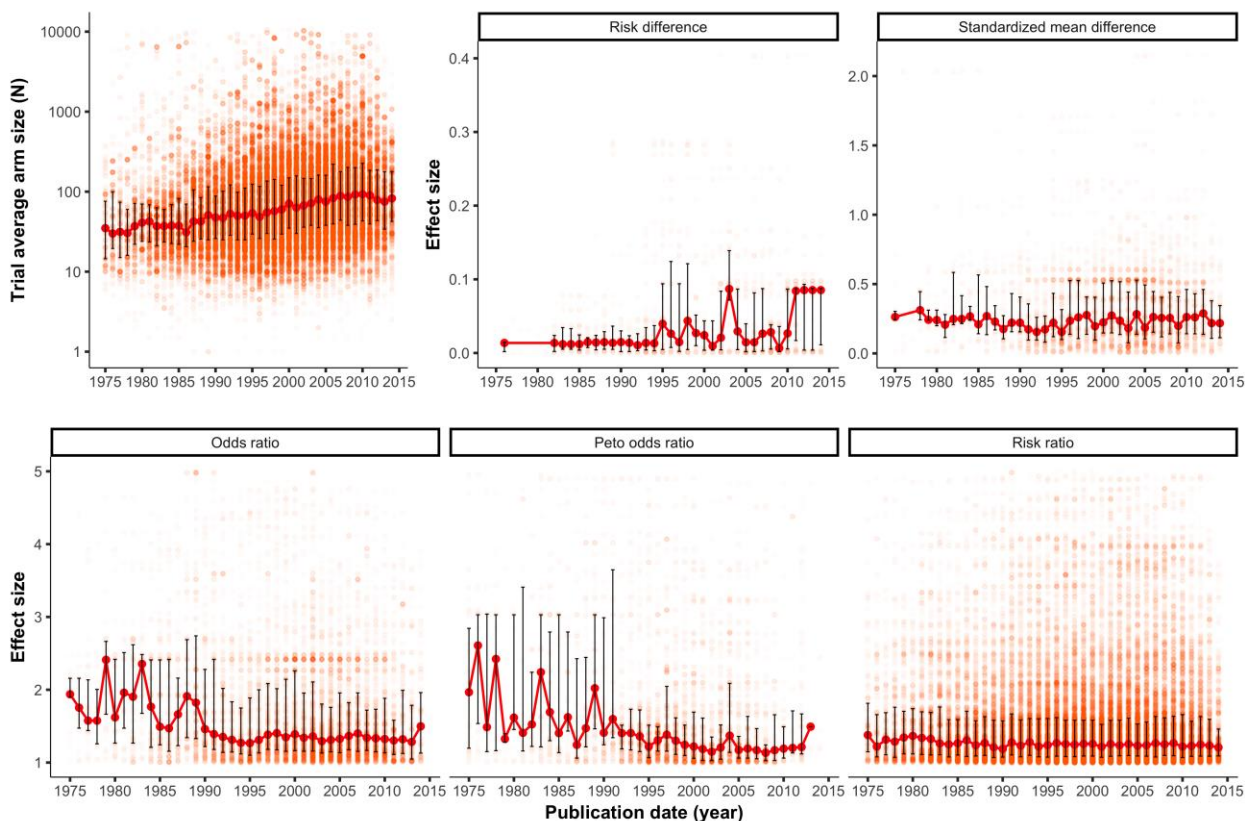


Figure 2 | The number of participants (N) enrolled in each trial arm, between 1975 and 2014 in red semi-transparent dots (top left). Corresponding effect sizes – classified in Cochrane reviews as risk difference, standardized mean difference, (Peto) odds ratio or risk ratio – are shown in the remaining plots. Median and interquartile data are plotted annually. Years with less than ten studies with the specific measure were omitted from the plot.

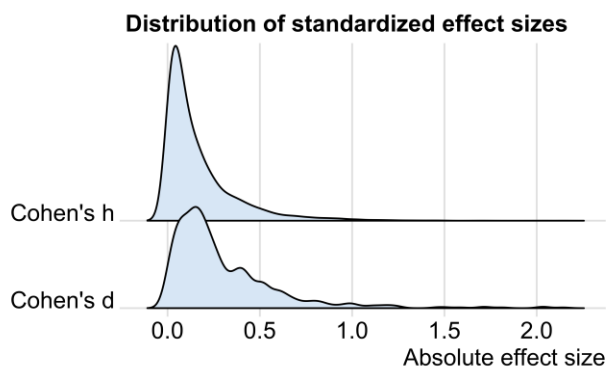


Figure 3 | Distribution plot of standardized effect sizes, based on the meta-analytic effect size from all meta-analyses. Cohen's h was based on the proportion of events in the meta-analysis in case of dichotomous study outcomes. In studies comparing means the standardized mean difference (Cohen's d) of the meta-analysis was directly available in the Cochrane database.

Table 2 | Median effect sizes for all meta-analyses

| Reported effect measure | N meta-analyses (n included trials) | Raw effect size: median (IQR) | Standard effect size* |
|------------------------------|-------------------------------------|-------------------------------|-----------------------|
| Odds ratio | 1,798 (17,772) | 1.37 (1.15-1.93) | } 0.09 (0.04-0.22) |
| Peto odds ratio | 783 (8,421) | 1.31 (1.11-1.79) | |
| Risk ratio | 8,459 (100,534) | 1.26 (1.09-1.64) | |
| Risk difference | 187 (2,275) | 0.02 (0.00-0.06) | } 0.09 (0.04-0.22) |
| Standardized mean difference | 625 (7,210) | 0.20 (0.11-0.40) | |

Median effect sizes are computed based on the meta-analysis; every meta-analysis is taken into account once irrespective of the number of included trials. To obtain a meaningful summary statistic, effect sizes were transformed to be unidirectional: the absolute number of risk differences and standardized mean differences was taken, and for (Peto) odds ratios and risk ratio's effects below one were inversed (1 divided by the effect, e.g. an RR of 0.5 becomes 2.0). These transformations only change the direction and not the magnitude of the effect.

N = number of meta-analyses (number of included studies)

*standard effect size: Cohen's d or h

4. Discussion

The current study provides an overview of the statistical power in 136,212 clinical trials across all medical fields. Our analyses demonstrate that effect sizes are small-, and that sample sizes of most clinical trials are too small to detect such an effect. Only 7% of individual trials had sufficient power to detect the observed effect from its respective meta-analysis. Though there is considerable room for improvement, an encouraging trend is the number of trials with sufficient power has increased over four decades from 5% to 9%, and from 9% to 15% in trials from significant meta-analyses. On average, sample sizes have doubled between 1975 and 2014 whereas effect sizes did not increase over time.

The distribution of effect sizes (with a median Cohen's h of 0.09 and a median Cohen's d of 0.20, respectively) shows that large effects are rare. This information should be taken into account when designing a clinical trial and determining the required minimum sample size. The effect size summary statistics provided here could also be used as standard prior in Bayesian modelling in medical research, since they are based on many thousands of trials covering the general medical field.

Our results are in agreement with a study by Turner and colleagues in which they also used the Cochrane database of systematic reviews (2008 version) to describe study power in clinical trials³. This study also showed low study power with a bimodal pattern of many low-powered studies and a small proportion of well-powered studies. The Turner study demonstrated a median power of 8%, whereas we find a comparable median power of 9% across all meta-analyses. This slightly higher percentage could be explained by the inclusion of more recent high-powered studies, or the exclusion of meta-analyses with less than five trials.

Our use of meta-analytic effect sizes to compute study power has two important shortcomings. First, although it is a fair –and the only available– approximation of the true effect of a given therapy, power and sample size calculations are designed to be performed a-priori. We would fully endorse that for an individual study there is no space for a post-hoc power computation. Second, it may be questioned whether statistical power can be computed when the estimation of the effect size includes a null-effect in the 95% confidence interval. If there is no effect, a power calculation cannot be performed. If the null-hypothesis: “there is no effect” cannot be rejected, there is no clear effect size estimation available as the basis for the power calculation. We have therefore also included all results for the subset of significant meta-analyses.

By analysing the temporal pattern across four decades, we identified an increase of study power over time. Moreover, since effect size estimates remained stable across time, our study clearly shows the need to increase sample sizes to design well-powered studies. A study on sample sizes determined in preregistration on ClinicalTrials.gov between 2007-2010 showed that over half of the registered studies included a required sample of 100 participants or less in their protocol¹⁷. We found that, within the published trials that have been included in a Cochrane meta-analysis, the findings are in line with these results, and although the average sample size has doubled since the 1970’s, and median sample size in 2010–2014 was between 150-180.

An argument in defence of performing small (or underpowered) studies has been made based on the idea that small studies can be combined in a meta-analysis to increase power. Halpern and colleagues already explained the invalidity of this argument in 2002¹, most importantly because small studies are more likely to produce results with wide confidence intervals and large p-values, and thus are more likely to remain unpublished. An additional risk of conducting uninformative studies is that a lack of an effect due to low power might decrease the interest by

other research teams to examine the same effect. A third argument against performing small studies is given in a study by Nuijten and colleagues⁷, which indicates that the addition of a small, underpowered study to a meta-analysis may actually increase the bias of an effect size instead of decreasing it.

There are several limitations to consider in the interpretation of our results. First, the outcome parameter studied in the meta-analysis may be different than the primary outcome of the original study; it may have been adequately powered for a different outcome parameter. This could result in lower estimates of average power, although it seems unlikely that the average effect size of the primary outcomes is higher than the effect sizes in the Cochrane database. Second, in contrast, effect sizes from meta-analyses are considered to be an overestimation of the true effect because of publication bias^{7,18}. Lastly, in determining the required power for a study a ‘one size fits all’ principle does not necessarily apply as Schulz & Grimes¹⁹ also argue. However, although conventions are always arbitrary¹² a cut-off for sufficient power at 80% is reasonable.

With statistical power consistently increasing over time, our data offer perspective and show that we, the scientific community, are heading in the right direction. Nevertheless, it is clear that most clinical trials remain underpowered. Although there may be exceptions justifying small clinical trials, we believe that in most cases underpowered studies are problematic. Clinical trials constitute the backbone of evidence-based medicine, and individual trials would ideally be interpretable in isolation, without waiting for a future meta-analysis. To further improve the current situation, trial pre-registrations could include a mandatory section justifying the sample size, based on realistic expectations of the effect size, and preferably with explicit reference to earlier published results in the same field. If no prior literature exists for the specific condition or treatment, we recommend that small effects should be assumed. Large-scale collaborations with

the aim of performing either a multi-centre study or a prospective meta-analysis may also increase sample sizes when individual teams lack the resources to collect larger sample sizes. Another important way to introduce long-lasting change is by improving the statistical education of current and future scientists ⁵. Even though our analyses demonstrate that sufficient power in clinical trials is still problematic, the situation seems to be slowly improving. Together, these results encourage further efforts to increase statistical power in clinical trials to guarantee rigorous and reproducible evidence-based medicine.

5. Funding

This work was supported by The Netherlands Organisation for Health Research and Development (ZonMW) grant “Fostering Responsible Research Practices” (445001002). The funding source had no involvement in study design; the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

6. Declarations of interest: none

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Figure legends

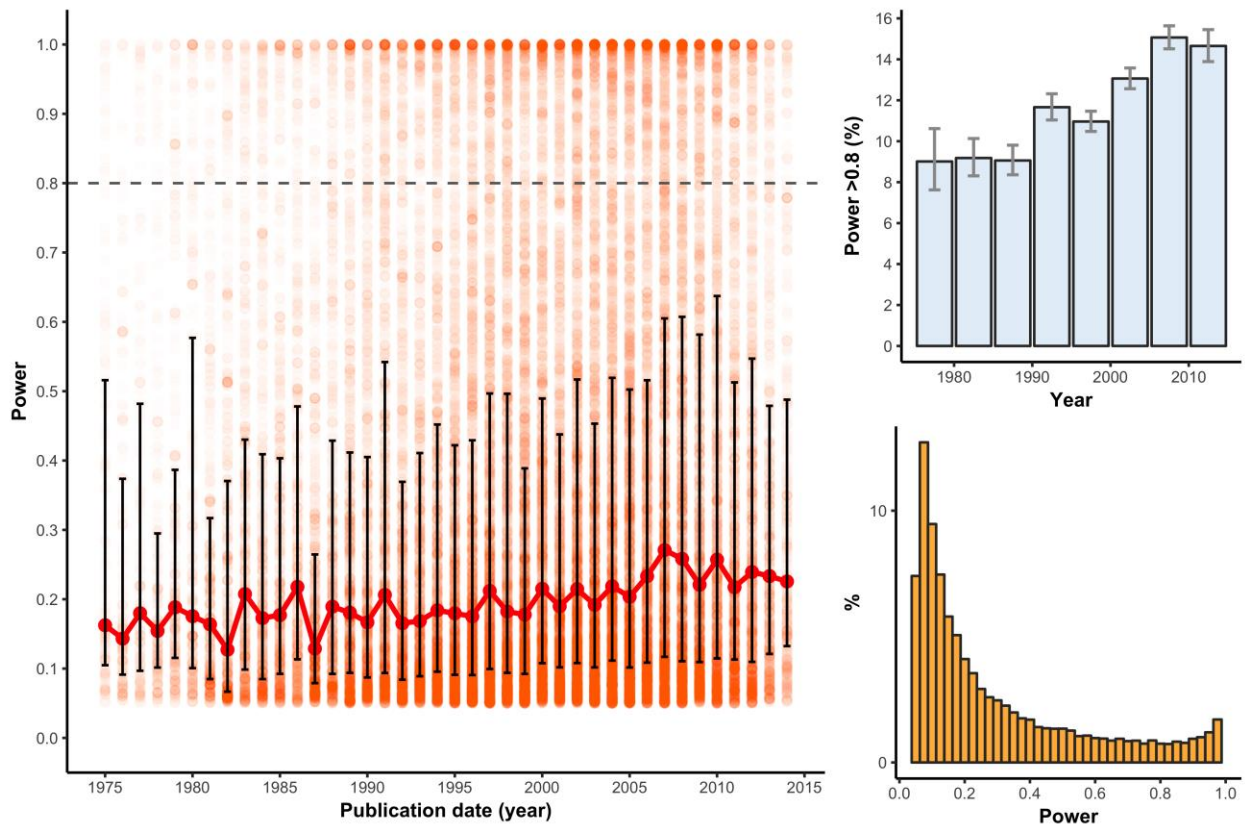
All figures should be printed in colour.

Figure 1 | Statistical power of clinical trials between 1975 and 2014 (left). Individual comparisons are shown as semi-transparent dots. Median power is shown in red with interquartile range as error bars. The percentage of adequately powered trial comparisons (i.e. $\geq 80\%$ power) is increasing over time (top right). The biphasic power distribution of the trials in general is apparent (bottom right).

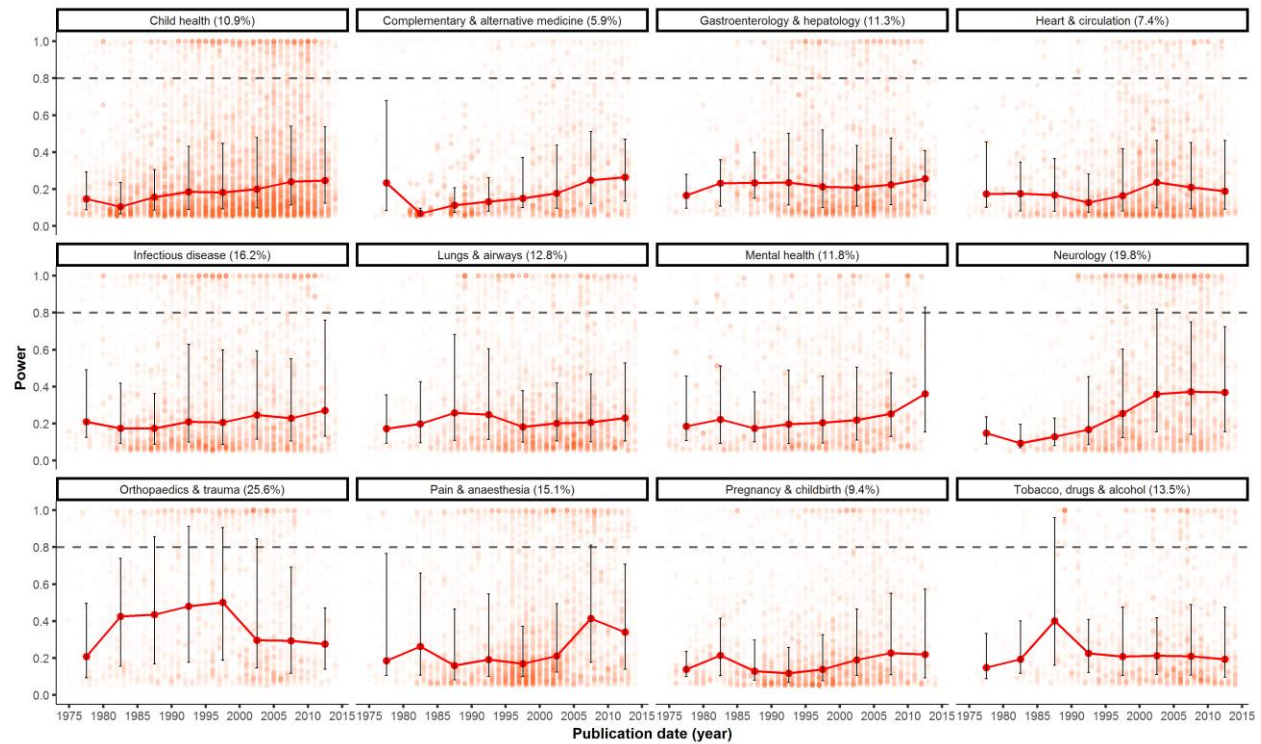
Figure 2 | The number of participants (N) enrolled in each trial arm, between 1975 and 2014 in red semi-transparent dots (top left). Corresponding effect sizes – classified in Cochrane reviews as risk difference, standardized mean difference, (Peto) odds ratio or risk ratio – are shown in the remaining plots. Median and interquartile data are plotted annually. Years with less than ten studies with the specific measure were omitted from the plot.

Figure 3 | Distribution plot of standardized effect sizes. Cohen's h was based on the proportion of events in the meta-analysis in case of dichotomous study outcomes. In studies comparing means the standardized mean difference (Cohen's d) of the meta-analysis was directly available in the Cochrane database.

SUPPLEMENTARY MATERIALS

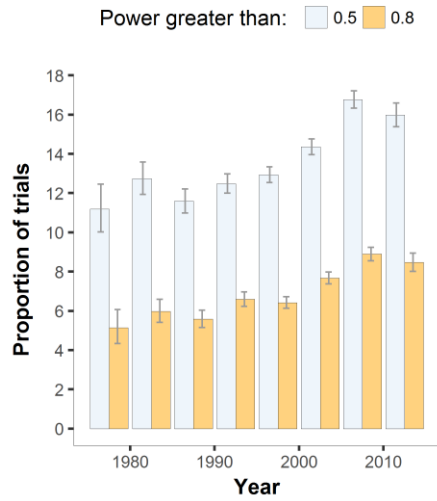


Supplementary Figure 1 | Statistical power of clinical trials between 1975 and 2014 from meta-analyses with p-value <0.05 (left). Individual comparisons are shown as semi-transparent dots. Median power is shown in red with interquartile range as error bars. The percentage of adequately powered trial comparisons (i.e. $\geq 80\%$ power) is increasing over time (top right). The biphasic power distribution of the trials in general is apparent (bottom right).

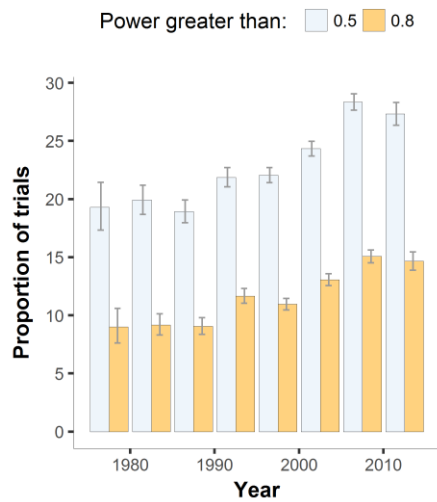


Supplementary Figure 2 | Statistical power of clinical trials between 1975 and 2014

across twelve major medical disciplines (disciplines with >4000 comparisons were included). Individual trial comparisons are visualized using red semi-transparent dots. Median and interquartile data is plotted and centred at five-year intervals. The percentage of adequately powered studies ($\geq 80\%$ power, indicated with dotted lines) over the entire period is plotted between parentheses following the disciplines' names.



A



B

Supplementary Figure 3 | Comparison of the percentage of trial comparisons with a minimum power of 0.5 and 0.8 over time. A = using all meta-analyses. B = using only significant meta-analyses.

Supplementary Table 1 | Median effect sizes for all meta-analyses with p-value <0.05

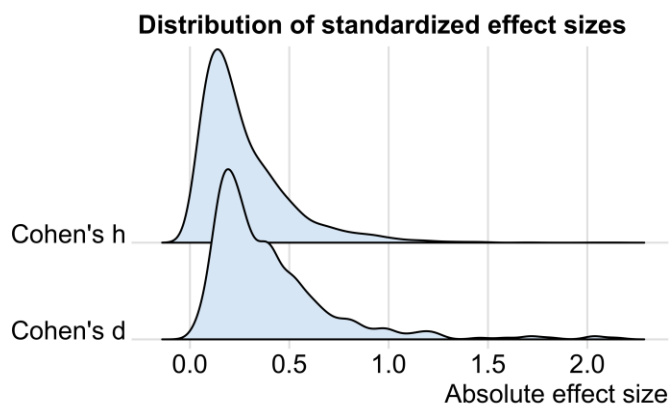
| Reported effect measure | N meta-analyses (n included trials) | Raw effect size: median (IQR) | Standard effect size* |
|------------------------------|-------------------------------------|-------------------------------|-----------------------|
| Odds ratio | 879 (10,234) | 1.83 (1.41-2.63) | } 0.21 (0.12-0.36) |
| Peto odds ratio | 348 (3,956) | 1.83 (1.43-2.92) | |
| Risk ratio | 4230 (57,633) | 1.57 (1.30-2.22) | |
| Risk difference | 68 (981) | 0.08 (0.04-0.14) | } 0.31 (0.19-0.51) |
| Standardized mean difference | 378 (5,143) | 0.31 (0.19-0.51) | |

Median effect sizes are computed based on the meta-analysis; every meta-analysis is taken into account once irrespective of the number of included trials. To obtain a meaningful summary statistic, effect sizes were transformed to be unidirectional: the absolute number of risk differences and standardized mean differences was taken, and for (Peto) odds ratios and risk ratio's effects below one were inversed (1 divided by the effect, e.g. an RR of 0.5 becomes 2.0). These transformations only change the direction and not the magnitude of the effect.

N = number of meta-analyses (number of included studies)

*standard effect size: Cohen's d or h

333



334

335 **Supplementary Figure 4** | Distribution plot of standardized effect sizes, based on the meta-
336 analytic effect size from all significant meta-analyses. Cohen's h was based on the proportion of
337 events in the meta-analysis in case of dichotomous study outcomes. In studies comparing means
338 the standardized mean difference (Cohen's d) of the meta-analysis was directly available in the
339 Cochrane database.

340

Supplementary Table 2 | Proportion studies with sufficient power and median power, through different methods of meta-analysis.

| Selected meta-analyses | Method | N meta-analyses (N studies) | Sufficient (≥ 0.8) power (95% CI) | Median power (IQR) |
|------------------------|----------|-----------------------------|--|--------------------|
| All | Original | 11,852 (136,212) | 7.3 (7.2-7.5) | 0.09 (0.06-0.26) |
| All | FE | 11,852 (136,212) | 7.2 (7.1-7.4) | 0.09 (0.06-0.26) |
| All | RE | 11,852 (136,212) | 7.5 (7.4-7.6) | 0.09 (0.06-0.26) |
| All | WLS-WAAP | 11,852 (136,212) | 7.2 (7.1-7.3) | 0.09 (0.06-0.26) |
| Significant | Original | 5,903 (77,947) | 12.4 (12.2-12.7) | 0.20 (0.10-0.48) |
| Significant | FE | 5,409 (73,533) | 12.9 (12.7-13.2) | 0.20 (0.09-0.49) |
| Significant | RE | 4,622 (65,156) | 14.2 (13.9-14.5) | 0.22 (0.10-0.54) |
| Significant | WLS-WAAP | 5,266 (70,720) | 12.4 (12.1-12.6) | 0.18 (0.09-0.47) |

CI: confidence interval. FE: fixed effects. IQR: interquartile range. Original: fixed- or random effects as performed in original meta-analysis. RE: random effects. WLS-WAAP: weighted least squares / weighted average of the adequately powered.

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